PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference MXI-301PC	**FOR FURTHER ACTION** see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US04/02725	International filing date (*day/month/year*) 30 January 2004 (30.01.2004)	(Earliest) Priority Date (*day/month/year*) 31 January 2003 (31.01.2003)
Applicant MEDAREX, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the Report**
   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
      ☐ The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. ☒ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.
2. ☐ **Certain claims were found unsearchable** (See Box No. II)
3. ☐ **Unity of invention is lacking** (See Box No. III)
4. With regard to the **title**,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. With regard to the **drawings**,
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      ☐ as suggested by the applicant.
      ☐ as selected by this Authority, because the applicant failed to suggest a figure.
      ☐ as selected by this Authority, because this figure better characterizes the invention.
   b. ☒ none of the figures is to be published with the abstract.

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Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:
   a. type of material
      - ☒ a sequence listing
      - ☐ table(s) related to the sequence listing

   b. format of material
      - ☐ in written format
      - ☒ in computer readable form

   c. time of filing/furnishing
      - ☒ contained in the international application as filed
      - ☒ filed together with the international application in computer readable form
      - ☐ furnished subsequently to this Authority for the purposes of search

2. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
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A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61K 39/00, 39/38, 39/395, 39/42;C07K 17/00, 16/00; C12P 21/08
US CL : 424/134.1,136.1,141.1,143.1,144.1,184.1,185.1,192.1;530/350,387.1,387.3
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 424/134.1,136.1,141.1,143.1,144.1,184.1,185.1,192.1;530/350,387.1,387.3

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 01/85798 A2 (DEO et al.) 15 November 2001, see entire document	1-49
Y	US 5,869,057 A (ROCK) 09 February 1999, see entire document	1-49
Y	US 2002/0187131 A1 (HAWIGER et al.) 12 December 2002, see entire document	1-49

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
03 December 2004 (03.12.2004)

Date of mailing of the international search report
03 JAN 2005

Name and mailing address of the ISA/US
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Authorized officer
Michael Szperka
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Jean Proctor
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Continuation of B. FIELDS SEARCHED Item 3:
MEDLINE EMBASE SCISEARCH BIOSIS CAPLUS EAST A_Geneseq SwisProt TrEMBL
antibody, human chorionioc gonadotropin, dendritic cell, APC, fusion protein

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
GIULIO A. DECONTI
LAHIVE & COCKFIELD LLP
28 STATE STREET
BOSTON, MA 02109

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing (*day/month/year*)	03 JAN 2005
Applicant's or agent's file reference: MXI-301PC	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/US04/02725	30 January 2004 (30.01.2004)	31 January 2003 (31.01.2003)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): A61K 39/00, 39/38, 39/395, 39/42;C07K 17/00, 16/00; C12P 21/08 and US Cl.: 424/134.1,136.1,141.1,143.1,144.1,184.1,185.1,192.1;530/350,387.1,387.3

Applicant

MEDAREX, INC.

1. This opinion contains indications relating to the following items:

- [x] Box No. I — Basis of the opinion
- [ ] Box No. II — Priority
- [ ] Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [ ] Box No. IV — Lack of unity of invention
- [x] Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI — Certain documents cited
- [ ] Box No. VII — Certain defects in the international application
- [ ] Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis(b)* that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Michael Szperka Jean Proctor Paralegal Telephone No. (571) 272-1600

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY	International application No. PCT/US04/02725

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material

   ☐ in written format

   ☒ in computer readable form

   c. time of filing/furnishing

   ☒ contained in international application as filed.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
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Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-49	YES
	Claims	NONE	NO
Inventive step (IS)	Claims	NONE	YES
	Claims	1-49	NO
Industrial applicability (IA)	Claims	1-49	YES
	Claims	NONE	NO

2. Citations and explanations:

Claims 1-49 lack an inventive step under PCT Article 33(3) as being obvious over Deo et al. (WO 01/85798) or Hawiger et al. (US 2002/0187131) in view of Rock (US Patent No. 5,869,057).

Deo et al. teach fusion proteins consisting of antibodies that specifically bind dendritic cells joined to various molecules, including tumor cell antigens, microbial antigens, and other autoantigens (see entire document, particularly page 5, lines 9-17). Such antigens are targeted to the dendritic cell by the antibody moiety, and epitopes from the antigen will then be presented on MHC class I and II molecules displayed on the surface of the dendritic cell for the purpose of initiating an immune response from T lymphocytes (see particularly page 5, lines 18-27). Specific sequences of antibodies useful for targeting dendritic cells are disclosed, and these antibodies can be co-administered with other immunomodulatory agents, such as cytokines including GM-CSF (see particularly page 57, lines 11-16). This reference differs from the claimed invention in that the specific antigen β human chorionic gonadotropin is not disclosed as being linked to an antibody by Deo et al.

Hawiger et al. teach the delivery of antigens to dendritic cells by conjugating antigens to antibodies that specifically target dendritic cells (see entire document, particularly the abstract). Dendritic cell molecules that are to be targeted by antibodies include DEC-205, the Fcγ receptor and the mannose receptor (see particularly paragraph 8). The antibody fusion proteins of Hawiger et al. can be administered with various cytokines that induced the maturation of dendritic cells (see particularly paragraphs 55-60). Antibodies that bind markers on dendritic cell and that are examples of antibodies suitable for use in their invention are also disclosed (see particularly paragraph 42). The antigens coupled to such antibodies will be presented on MHC class I and class II molecules to T cells and will result in an enhanced anti-cancer antigen immune response (see particularly paragraph 43). Antigens associated with many diseases and cancers are disclosed as being suitable for use with their invention (see particularly paragraph 46). This reference differs from the claimed invention in that it does not disclose β human chorionic gonadotropin as a tumor antigen.

Rock teaches the generation of a fusion protein consisting of β human chorionic gonadotropin linked to a bacterial protein for the purpose of treating human diseases (see entire document, particularly the abstract). Rock also teaches that β human chorionic gonadotropin in expressed by many tumors, including metastatic cancers, but is not normally expressed otherwise except during pregnancy. As such, immunization against hCG can be used as an antimetastasis treatment (see particularly column 5, line 30 to column 8, line 37). Using hCG as a tumor antigen allows for the targeting of metastatic tumors, a group of cancers that are otherwise difficult to treat (see particularly the paragraph that spans columns 5 and 6).

Therefore, a person of ordinary skill in the art would have been motivated to make the obvious substitution of hCG, a known tumor antigen as taught by Rock, for the antigens used in the anticancer dendritic cell targeting antibody-antigen fusion constructs taught by both Deo et al. and Hawiger et al. for the purpose of treating cancers, including metastatic cancers, that are otherwise difficult to treat effectively.

Claims 1-49 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.